

### **Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

### **Listing of Claims:**

1. (Currently Amended) A composition having an amphipathic characteristic comprising a hydrophilic portion and a hydrophobic portion joined by an ortho ester linker ~~having an amphipathic characteristic~~, wherein the ortho ester linker hydrolyzes at an increasing rate as the pH is reduced below 7, wherein hydrolysis cleavage of the ortho ester linker directly detaches the hydrophobic portion and eliminates the amphipathic characteristic, [[and]] wherein the hydrophilic portion is selected from the group consisting of methoxypolyethylene, polyethyleneglycol, hydroxylated dendrons, poly(methyloxazoline), poly(ethyloxazoline) and polyvinylpyrrolidone and wherein the hydrophobic group is selected from the group consisting of diacyl glycerols, distearoylglycerol, dipalmitoylglycerol, dimyristoyl glycerol, dioleoyl glycerol, tocopherol, cholesterol, coenzyme Q, and ceramide.
2. (Original) The composition of claim 1, wherein the hydrophilic portion comprises a polymer capable of increasing circulation time in the bloodstream of animals when incorporated on the surface of an encapsulator.
3. (Cancelled)
4. (Cancelled)
5. (Original) The composition of claim 2, wherein the hydrophilic portion comprises polyethyleneglycol having a molecular weight from 200 to 20000.
6. (Previously Presented) The composition of claim 19, wherein the hydrophilic portion comprises a targeting ligand.

7. (Previously Presented) The composition of claim 19, wherein the hydrophilic portion comprises a cationic group.

8. (Cancelled)

9. (Cancelled)

10. (Original) The composition of claim 1, wherein the hydrophobic portion is selected from the group consisting of tocopherol, cholesterol, coenzyme Q, and ceramide.

11. (Original) The composition of claim 1, wherein the ortho ester linker comprises a diortho ester.

12. (Previously Presented) The composition of claim 11, wherein the ortho ester linker comprises a diketene acetal group.

13. (Original) The composition of claim 11, wherein the ortho ester linker comprises a 3,9-dialkoxylated 3,9-Diethyl-2,4,8,10-tetraoxaspiro[5,5]undecane derivative.

14. (Original) The composition of claim 11, wherein the composition comprises 3,9-Diethyl-3-(2,3-distearoyloxypropyloxy)-9-(methoxypolyethyleneglycol2000-1-yl)-2,4,8,10-tetraoxaspiro[5,5]undecane.

15. (Previously Presented) The composition of claim 19, wherein the ortho ester linker comprises a single ortho ester.

16. (Currently Amended) The composition of claim 15, wherein the ortho ester linker comprises a dichloromethylmethyl ether ~~derivative~~ and the hydrophilic portion is cationic.

17. (Original) The composition of claim 16, wherein the composition comprises *N,N*-dimethyl-(4-methoxy-(cholest-5-en-3 $\beta$ -oxy)hept-3,5-dioxa-yl)ammonium (DOC).

18. (Original) The composition of claim 16, wherein the composition comprises *N,N,N*-trimethyl-(4-methoxy-(cholest-5-en-3 $\beta$ -oxy)hept-3,5-dioxa-yl)amine iodide.

19. (Currently Amended) A composition comprising an encapsulator selected from the group consisting of liposomes, emulsions, micelles and lipidic bodies, wherein the encapsulator comprises ~~an amphipathic molecule having a~~ conjugate having an amphipathic characteristic with a hydrophilic portion and a hydrophobic portion capable of anchoring the ~~amphipathic molecule~~ conjugate to the encapsulator, wherein the ~~amphipathic molecule is~~ hydrophilic portion and the hydrophobic portion are joined by an ortho ester linker, wherein the ortho ester linker hydrolyzes and cleaves at an increasing rate as the pH is reduced below 7 and wherein cleavage of the ortho ester directly detaches the hydrophilic portion from the hydrophobic portion and the encapsulator, eliminates the amphipathic characteristic and destabilizes the encapsulator.

20. (Original) The composition of claim 19, wherein the encapsulator further comprises a lipid.

21. (Original) The composition of claim 20, wherein the lipid comprises DOPE.

22. (Previously Presented) The composition of claim 21, comprising DOPE/methoxypolyethylene glycol 2000-diortho ester-distearoyl glycerol conjugate (POD) in a ratio of about 97:3 to 85:15.

23. (Previously Presented) The composition of claim 21, comprising DOPE/dimethylethanolamine-ortho ester-cholesterol (DOC).

24. (Original) The composition of claim 20, wherein the lipid comprises a fusogenic lipid.

25. (Original) The composition of claim 20, wherein the lipid comprises a lipid selected from the group consisting of phosphatidylcholine, phosphatidylglycerol,

phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, cholesteryl hemisuccinate, cholesterol sulfate, ceramide, cardiolipid, *N*[1-,2dioleoyl-3-trimethyl]ammonium propane (DOTAP), dimethyldioctadecylammonium bromide (DDAB), 1-palmitoyl-2-oleoyl-sn-glycero-3-ethyl-phosphocholine, *N*[1-(2,3-dioleyloxy)propyl]-*N,N,N*,-triethylammonium (DOTMA), triglycerides, squalene, coenzyme Q and alkyl acylcarnitine esters.

26. (Original) The composition of claim 20, wherein the lipid further comprises a targeting ligand.

27. (Original) The composition of claim 26, wherein the targeting ligand is selected a group consisting of hyaluronan, antibodies, peptides, folate, receptor antagonists, carbohydrates, transferrin, protein hormones, and cytokines.

28. (Original) The composition of claim 19, wherein the hydrophilic portion comprises a targeting ligand.

29. (Original) The composition of claim 28, wherein the targeting ligand is selected a group consisting of hyaluronan, antibodies, peptides, folate, receptor antagonists, carbohydrates, transferrin, protein hormones, and cytokines.

30. (Currently Amended) An encapsulator for delivering a compound, comprising an ~~amphipathic~~ a low pH sensitive lipidic composition having an amphipathic characteristic and comprising an ortho ester linker wherein the encapsulator exhibits degradation of less than 10% within 3 hours at a pH of 7.4 and degradation greater than 50% within 60 min at a pH of 5.0, wherein the encapsulator is selected from the group consisting of liposomes, emulsions, micelles and lipidic bodies and wherein hydrolysis and cleavage of the ortho ester linker directly detaches a hydrophilic portion of the lipidic composition from a hydrophobic portion of the lipidic composition and the encapsulator to eliminate the amphipathic characteristic and destabilize the encapsulator.

31. (Original) The encapsulator of claim 30, wherein the amphipathic low-pH sensitive lipidic composition comprises a hydrophilic portion, a hydrophobic portion and an ortho ester linker.

32. (Original) The encapsulator of claim 31, wherein the hydrophilic portion comprises PEG.

33. (Previously Presented) The encapsulator of claim 32, wherein the ortho ester linker comprises a diortho ester.

34. (Original) The encapsulator of claim 30, further comprising a lipid.

35. (Original) The encapsulator of claim 30, wherein the lipid is selected from the group consisting of phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, cholesteryl hemisuccinate, cholesterol sulfate, ceramide, cardiolipid, *N*[1-,2dioleoyl-3-trimethyl]ammonium propane (DOTAP), dimethyldioctadecylammonium bromide (DDAB), 1-palmitoyl-2-oleoyl-sn-glycero-3-ethyl-phosphocholine, *N*[1-(2,3-dioleoyloxy)propyl]-*N,N,N*, -triethylammonium (DOTMA), triglycerides, squalene, coenzyme Q and alkyl acylcarnitine esters, and dioleoylphosphatidyl ethanolamine (DOPE).

36. (Original) The encapsulator of claim 33, wherein the hydrophilic portion comprises PEG, further comprising a lipid.

37. (Original) The encapsulator of claim 30, wherein the ortho ester linker comprises a dialkoxy methoxy methine group.

38. (Currently Amended) A method for delivering a drug to a cell comprising the steps of providing an encapsulator comprising a lipidic ortho ester conjugate (LOC) having an amphipathic characteristic and the drug, wherein the encapsulator is selected from the group consisting of liposomes, emulsions, micelles and lipidic bodies, wherein hydrolysis and cleavage

of an ortho ester linker directly detaches a hydrophilic portion of the lipidic ortho ester conjugate from a hydrophobic portion of the lipidic ortho ester conjugate and the encapsulator to eliminate the amphipathic characteristic and destabilize the encapsulator and administering the encapsulator.

39. (Previously Presented) The method of claim 38, further comprising the steps of exposing the encapsulator to reduced pH, degrading the encapsulator and releasing the drug.

40. (Original) The method of claim 38 further comprising the steps of preparing a dry powder formulation of the encapsulator and administering the dry powder.

41. (Original) The method of claim 40, further comprising the steps of preparing a dry powder formulation of the encapsulator, rehydrating the encapsulator in an appropriate buffer and administering the encapsulator.

42. (Currently Amended) A method for incorporating a lipidic ortho ester conjugate (LOC) having an amphipathic characteristic into an encapsulator, the ~~encapsulator~~ lipidic ortho ester conjugate comprising an ortho ester linker wherein hydrolysis and cleavage of the ortho ester linker directly detaches a hydrophilic portion of the lipidic ortho ester conjugate from a hydrophobic portion of the lipidic ortho ester conjugate and the encapsulator to eliminate the amphipathic characteristic and destabilize the encapsulator, comprising the step of mixing the encapsulator with the lipidic ortho ester conjugate (LOC).

43. (Previously Presented) The method of claim 42, further comprising the steps of:

- a) preparing a dry film of the lipidic ortho ester conjugate (LOC);
- b) rehydrating the a lipidic ortho ester conjugate (LOC) to form micelles; and
- c) combining the micelles with an encapsulator suspension.

44. (Previously Presented) The method of claim 42, wherein the encapsulator comprises a cationic lipoplex further comprising the steps of preparing a cationic lipoplex and coating the lipoplex with the lipidic ortho ester conjugate (LOC).

45. (Previously Presented) The method of claim 42 further comprising the steps of:
- preparing a dry film of the lipidic ortho ester conjugates (LOC);
  - preparing an encapsulator suspension; and
  - combining the encapsulator suspension with the dry film.
46. (Previously Presented) The method of claim 42, further comprising the steps of:
- preparing the lipidic ortho ester conjugate (LOC) in a non-aqueous, water miscible solvent
  - preparing an encapsulator suspension; and
  - combining the encapsulator suspension with the lipidic ortho ester conjugate (LOC) in the water miscible solvent.
47. (Previously Presented) The method of claim 46, wherein the non-aqueous, water miscible solvent is selected from the group consisting of acetonitrile, dimethylsulfoxide, glyme, methylpyrrolidone, ethanol, triacetin and mixtures of these.
48. (Currently Amended) A method for storing an encapsulator for delivering a compound, comprising the steps of:
- providing an encapsulator comprising ~~an amphipathic~~ a low pH sensitive lipidic compound comprising an amphipathic characteristic and an ortho ester linker wherein the encapsulator exhibits degradation of less than 10% within 3 hours at a pH of 7.4 and degradation greater than 50% within 60 min at a pH of 5.0 and wherein hydrolysis and cleavage of the ortho ester linker directly detaches a hydrophilic portion of the lipidic ortho ester conjugate from a hydrophobic portion of the lipidic ortho ester conjugate and the encapsulator to eliminate the amphipathic characteristic and destabilize the encapsulator; and
  - lyophilizing the encapsulator.
49. (Original) The method of claim 48, further comprising the step of milling the lyophilized encapsulator to form a dry powder.

50. (Currently Amended) A method for gene transfer comprising the steps of:

- a) providing an encapsulator comprising ~~an amphipathic~~ a low pH sensitive lipidic composition having an amphipathic characteristic, an acid labile ortho ester bond and a polynucleotide, wherein hydrolysis and cleavage of the ortho ester linker directly detaches a hydrophilic portion of the lipidic composition from a hydrophobic portion of the lipidic composition and the encapsulator to eliminate the amphipathic characteristic and destabilize the encapsulator;
- b) administering the encapsulator to an animal;
- c) exposing the encapsulator to reduced pH to degrade the encapsulator; and
- d) releasing the polynucleotide.

51. (Original) The method of claim 50, further comprising the step of forming a dry powder formulation from the encapsulator prior to administering the encapsulator.

52. (Original) The method of claim 51, further comprising the step of rehydrating the encapsulator prior to administering the encapsulator.